

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Asthma Mortality in Australia in the 21st Century: a case series analysis
AUTHORS	Goeman, Dianne; Abramson, Michael; McCarthy, Edwina; Zubrinich, Celia; Douglass, Jo

VERSION 1 - REVIEW

REVIEWER	Gonzalez-Barcala, Francisco University Hospital of Santiago de Compostela, Department of respiratory Diseases
REVIEW RETURNED	21-Jan-2013

GENERAL COMMENTS	<p>1. Is the question posed original, important and well defined?</p> <p>To analyse the causes of death due to asthma is an interesting topic, with few studies in the literature. Improved knowledge of this could lead to better management of the disease.</p> <p>The main objective of this work is clearly explained by the authors.</p> <p>2. Are the data sound and well controlled?</p> <p>See point 4.</p> <p>3. Is the interpretation (discussion and conclusion) well balanced and supported by the data?</p> <p>The discussion seems a bit speculative.</p> <p>Firstly, some comments on the health system of the country studied are needed. Access to the health system in countries with free universal public health care, like those in Western Europe, is not the same as in others where private insurance predominates, as in the USA.</p> <p>Page 14, line 56- In 243/283 cases, it is believed the cause of death is asthma, as indicated in the Death Registers. This seems to support the high specificity of the death certified as asthma. You could mention this.</p>
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Page 15- line 19- it says “our findings identify disadvantage as an underlying theme among asthma deaths”. However, in the results, it was not analysed if there was a relationship between disadvantage and death due to asthma or preventable death.

Page 15- line 39- it says “our study confirms higher rates of asthma deaths in those living in areas of disadvantage...”. But this has not been analysed. That the majority of deaths occur in areas of disadvantage does not indicate that there may be a higher risk for asthma here, given that we do not know the prevalence of the disease in these areas, nor does it give the number of inhabitants.

Page 17- Line 3. It says that “deaths occurred in public places indicates rapid onset asthma attacks”. This does not seem to be mentioned by the authors who analysed “rapid-onset attacks” (Plaza V, reference19; Rodrigo G, reference 18; Kolbe, Thorax 1998). There could have been multiple factors for deaths to occur in public places, besides a rapid-onset attack.

Page 18- line 23. It says “Ownership of written action plans has declined”. However in Results, page 13-line 25- it is stated “It was not possible to determine written action plan ownership from this data set.”

CONCLUSIONS:

They must be re-written in accordance with that indicated in the Results and Discussion.

For example: Page 19- line 19. It says “Our retrospective study provides a current assessment of death from asthma across Australia.”. It should be added that it is among the deaths”, given that they may be different from the deaths due to asthma that are not reported by the Coroner.

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?

In this section, it must clearly indicate the period of the study (although it is mentioned in the Results), and the retrospective nature of the study.

	<p>It should be clearly explained what information could be consulted, particularly if they are included in the hospital or general practitioner clinical notes.</p> <p>Clearly mention the comorbidities that are considered as exclusion criteria (if there were any).</p> <p>The SEIFA index must be explained for readers of other countries, who are not used to using it. Between which values scored, what is a significant change in score...</p> <p>STATISTICAL ANALYSIS:</p> <p>Seems a little lacking. A multivariate analysis would provide more information on what really are the significant factors. There could be a correlation between the SEIFA-delay seeking help-illegal drug use- inadequate management index.... Or even with other comorbidities not analysed but may be a known risk factor for a poor prognosis of the asthma (obesity...).</p> <p>The opinion of a reviewer expert in statistics-epidemiology could be useful.</p> <p>5. What are the strengths and weaknesses of the methods?</p> <p>The main strength of the study is providing toxicological and the post-mortem information, which reinforces the accuracy of the causes of death.</p> <p>As weak ones, see points 3, 4, 6.</p> <p>6. Can the writing, organization, tables and figures be improved?</p> <p>RESULTS:</p> <p>Almost 50% of the cases are lost. The main reasons for these losses should be explained, since it could lead to a</p>
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bias.

Also, the toxicology analysis was unavailable in 75 cases (47%). The reasons should be given, since it could lead to inclusion biases.

Table 2 should show the rates, as well as the absolute values. The number of cases acquire a value in relation to the population of each region.

PAGE 10- Line 38: PREVENTABLE DEATHS:

It should be easier to read: ...70% of the cases (169/243) instead of “One hundred and sixty-nine of the 243(70%) cases”

A table could be added with the preventable /modifiable factors, at least those with the higher frequencies.

Page 10-Case characteristics.

It would be more useful to present a table comparing the characteristics of the cases with preventable or modifiable factors vs. cases with non- preventable-non-modifiable factors, and analysing whether there were significant differences.

	Preventable or modifiable factors	Non-preventable-non-modifiable factors	<i>P</i>
Age	54	48	0.9
Gender, male %	48%	52%	0.9
SEIFA	980	995	0.7
Location of death
Home			
Hospital-clinic			
Public places			
Residence			
Psychosocial issues			
.....

7. When revisions are requested.

I think that:

- data need to be added to support the authors' conclusions
- better justification is needed for the arguments based on existing data
- the clarity and/or coherence of the paper needs to be improved.

8. Are there any ethical or [competing interests](#) issues you would like to raise?

Ethically OK.

9. References:

References are quite old, 50% older than 5 years.

Reference 26 is not required, since it is included in Reference 25.

There are some important (and updated) references lacking, or which could be useful to improve the manuscript.

- Wilson DH, Tucker G, Frith P, Appleton S, Ruffin RE, Adams RJ. Med J Aust. 2007 Apr 16;186(8):408-11.
- Wijesinghe M, Weatherall M, Perrin K, Crane J, Beasley R. International trends in asthma mortality rates in the 5- to 34-year age group: a call for closer surveillance. Chest. 2009;135:1045-9.
- Finkelstein MM, Chapman KR, McIvor RA, Sears MR. Mortality among subjects with chronic obstructive pulmonary disease or asthma at two respiratory disease clinics in Ontario. Can Respir J. 2011;18:327-32.
- Bartolomei-Díaz JA, Amill-Rosario A, Claudio L, Hernández W. Asthma mortality in Puerto Rico: 1980-2007. J Asthma. 2011;48:202-9
- [Greenelch KM](#), [Kelly-Welch AE](#), [Shi Y](#), [Keegan AD](#). Chronic morphine treatment promotes specific Th2 cytokine production by murine T cells in vitro via a Fas/Fas ligand-dependent mechanism. [J Immunol](#). 2005 Oct 15;175(8):4999-5005. **Morphine increases TH2**

	<p style="color: red;">differentiation</p> <ul style="list-style-type: none"> ➤ Krantz AJ, Hershow RC, Prachand N, Hayden DM, Franklin C, Hryhorczuk DO. Heroin insufflation as a trigger for patients with life-threatening asthma. Chest. 2003 Feb;123(2):510-7. ➤ Boto de los Bueis A, Pereira Vega A, Sánchez Ramos JL, Maldonado Pérez JA, Ayerbe García R, García Jiménez D, Pujol de la Llave E. Bronchial hyperreactivity in patients who inhale heroin mixed with cocaine vaporized on aluminum foil. Chest. 2002 Apr;121(4):1223-30. Increase in BHR after inhaling heroin. ➤ Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. Thorax. 1998 Apr;53(4):241-7 Vital asthma risks are poorly perceived. ➤ Malmström K, Kaila M, Kajosaari M, Syvänen P, Juntunen-Backman K. Fatal asthma in Finnish children and adolescents 1976-1998: validity of death certificates and a clinical description. Pediatr Pulmonol. 2007 Mar;42(3):210-5. ➤ Jørgensen IM, Jensen VB, Bülow S, Dahm TL, Prahl P, Juel K. Asthma mortality in the Danish child population: risk factors and causes of asthma death. Pediatr Pulmonol. 2003 Aug;36(2):142-7. ➤ Lane WG, Newman D, Edwards M, Blaisdell C. Disparities in the circumstances of asthma deaths in Maryland. J Asthma. 2006 Dec;43(10):777-82
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REVIEWER	<p>Prof dr Dragica Pešut MD, PhD School of Medicine University of Belgrade Teaching Hospital of Lung Diseases Clinical Centre of Serbia 11000 Belgrade Visegradska 26 Serbia</p> <p>I declare no conflict of interest.</p>
REVIEW RETURNED	28-Jan-2013

GENERAL COMMENTS	In this retrospective descriptive study the authors used the National
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Coroner's Information System to search for codes J45 and J46 of the ICD-10 (International Classification of Diseases) between 2005 and 2009 as underlying cause of death together with available national mortality statistics bases. They describe epidemiological situation with asthma mortality in Australia with special regard to risk factors in all the cases where it was possible. In some settings, the proportion of such cases has reached only 49% available for the analysis. This is a serious limitation of retrospective studies in general and majority of mortality studies are like that. The authors have explained some limitations of the study that might contribute to possible underestimation of the overall contribution of asthma to adult deaths in Australia (cause of death analysis focuses on only one underlying cause rather than multiple causes of death).

One pattern seen in most regions of the world is an increase in asthma mortality rate with increasing age. Usual separate analysis of the ≥ 5 -34 age group that is missing in this study could bring much more light because the diagnosis of asthma mortality is firmly established for this age interval. Namely, it has been shown that in the ≥ 5 -34 year age group false-positive reporting (i.e. deaths from other causes falsely attributed to asthma) and false-negative reporting (i.e. asthma-related deaths falsely assigned to other categories) was extremely low. The accuracy of this approach declines with increasing age, with false positive reporting rates of $>30\%$ in those aged 65 years or more. The authors have excluded from the analysis the cases above the age of 70 years (and why not 65 and more following definition of the elderly; suppose that 10-year age intervals were available for the analysis). Even taking into consideration the decline in certification accuracy in older age groups, this does indicate a considerably greater risk of death in older asthmatics and the importance of care in this group.

Despite all the limitations, including difficulties in identification of certain proportion of the cases that might impact statistical analysis, the study of case series represents a precious contribution to the field of asthma mortality. It revealed higher rates of asthma deaths related to inequity, psychosocial issues, health literacy, alcoholism, and social isolation as well as living in rural and remote areas. Living in rural areas however has not been documented to be eventually associated to the related antigens presented in the area. Although 32% of Australians live in rural areas, the data are missing about the prevalence of asthma in this part of the population. In some cities in Europe, asthma prevalence rates are constantly higher in the surroundings and green areas than in the city urban centres. The authors could discuss this further - Is higher prevalence of asthma in Australian rural areas /if it is higher compared to urban ones/ a possible reason for found higher proportion of asthma related deaths in these areas?

The preventable factors are mentioned but it is not clear what preventable factors the authors had in mind. Some recent results support the existence of a genetic basis to the severe asthma phenotype, including asthma-related death, and this could be also mentioned in the discussion session.

List of 30 correctly cited references is included.

Table 2.

Despite the authors' explanation, time interval (2005-2009) should be the same for all the studied territories whatever small number of

	<p>the cases was found in Tasmania, NT and ACT (2005-2010).</p> <p>Minor spelling errors Page 6, 9: a increase should be an increase; Page 7, 52: The correct name of SPSS Statistical Package ...for Social 'Sciences' and not for 'Scientists'.</p>
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REVIEWER	<p>Dr Mark L Levy Senior Research Fellow, Allergy and Respiratory Research Group, Centre for Population Health Sciences: GP Section, University of Edinburgh. Doorway 3, Medical School, Teviot Place, Edinburgh EH8 9AG</p> <p>Potential competing interests: i) The opinions expressed above are my own, and are not in my official capacity in my current position of: Clinical Lead for the UK National Review of Asthma Deaths, due to report in 2014. www.rcplondon.ac.uk/projects/national-review-asthma-deaths 2) Emeritus Editor, Primary Care Respiratory Journal, www.thepcrj.org</p>
REVIEW RETURNED	02-Feb-2013

THE STUDY	<ul style="list-style-type: none"> - Line 26 page 6 does not define the population being studied. This needs to be refined (ie as far as I can see, about 20% of all asthma deaths in this time period in Australia (ie 283/1552 cases; I got confused by the numbers of asthma deaths in the text and tables including 1552; 557 and 283 on page 8; Table 2 totals were 563 - suggest add totals to the table)) - 'Circumstances surrounding the deaths' - I cant see in the methods how this is defined or ascertained - if the medical records were not available, then state how these are based on eg . third part reports from the police and coroners reports. - I got confused regarding the population being studied - in essence 283 cases (? out of 557) identified from the NCIS database of cases reported to the coroner. I suggest this is clarified. Particularly for a 'non-Australian' reader. - An intro to the system for certifying and confirming the accuracy of asthma deaths in Australia would help. What training do doctors have in completing death certificats? How is 'Underlying cause of death due to asthma determined? Which sorts of cases are referred to the coroners? Do the coroners do post mortems on all cases referred and what constitutes a post mortem exam - ie is histology always done? Is this quality controlled - eg are the conclusions agreed by more than one coroner? - The authors should define the outcomes more clearly. eg what are possble preventable factors? How did they 'confirm' the asthma deaths? (Page 6 lines 56/57). How did they confirm these people actually had asthma? As far as I can see, the clinical records were not available to this investigation - if so, some detailed analysis could be included in the section on 'Inadequate treatment', page 13. - Goldacre reference could be included. PDF File attached. (Goldacre MJ, Duncan ME, Griffith M. Death rates for asthma in English populations 1979-2007: Comparison of underlying cause and all certified causes. Public Health. 2012;126(5):386-93.) Suggest include some discussion on accuracy of death certificates. - Page 8 line 16 - what is a 'closed case'? Suggest define this term.
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RESULTS & CONCLUSIONS	<p>My assessment scores above may seem confusing - my difficulty is that the results are clearly written up as is the discussion, however, it took me a while to work out which population were actually studied - and I still dont know if the medical records were utilised in deriving the final conclusions. I can understand the results and the interpretation of these, however, as above the authors do need to improve on the introduction section: to clarify the systems in place in Australia for death certification; to describe the death certification process and the methodology and training of the coroners performing the post mortems in particular.</p> <p>The study population ie as I can see 20% of the certified asthma death cases in the time period studied should be clearly defined in the Methods section.</p> <p>The discussion should include details of the quality and robustness of the cases confirmed by the panel as 'underlying asthma deaths'.</p>
REPORTING & ETHICS	<p>No Consort Diagram - this would help to address my confusion regarding the study population.</p>
GENERAL COMMENTS	<p>As the revision required relates to clarifying the intro and methodology, and a few additions to the discussion, I think this paper should be published, after satisfactory revision.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

One pattern seen in most regions of the world is an increase in asthma mortality rate with increasing age. Usual separate analysis of the ≥5-34 age group that is missing in this study could bring much more light because the diagnosis of asthma mortality is firmly established for this age interval.

Namely, it has been shown that in the ≥5-34 year age group false-positive reporting (i.e. deaths from other causes falsely attributed to asthma) and false-negative reporting (i.e. asthma-related deaths falsely assigned to other categories) was extremely low.

The accuracy of this approach declines with increasing age, with false positive reporting rates of >30% in those aged 65 years or more.

The authors have excluded from the analysis the cases above the age of 70 years (and why not 65 and more following definition of the elderly; suppose that 10-year age intervals were available for the analysis). Even taking into consideration the decline in certification accuracy in older age groups, this does indicate a considerably greater risk of death in older asthmatics and the importance of care in this group.

Due to Australian Privacy Regulations, restrictions are placed on the use of data from the Registrars of Births, Deaths and Marriages. These restrictions prevented researchers accessing Death Certificates, and therefore accuracy of death certificates could not be examined in this study.

In July 2000, Australia became the only country in the world to have developed a national collection of coronial information – the National Coroners Information System (NCIS). Management of the NCIS and approval for access is undertaken by the Victorian Department of Justice.

The NCIS database records 'reportable' deaths (cases referred to the Coroner). A 'reportable' death being one that is considered 'unexpected' 'unnatural', 'violent' or the death of someone 'in care' at the time of death. Usually a police officer or a medical practitioner will notify the Coroner of any death that may be 'reportable'. However, any person may notify the Coroner if they believe that a reportable

death has occurred. The role of the Coroner is to investigate the circumstances surrounding all 'Reportable deaths'.

Once the Coroner has investigated the death, a finding is made and the case is closed and coded on the NCIS database according to International Classification of Disease and the Underlying Cause of Death is confirmed.

As we were unable to access asthma Deaths through the Registrars, we only examined cases that were on the NCIS and therefore had been considered 'unexpected', 'unnatural' or a person who had been in care at the time of death. As stated in the paper on page 19 under Study Limitations, a limitation of our data is that cases where a Medical Practitioner was willing to complete and sign the death certificate certifying the asthma death that was not 'unexpected' 'unnatural' or 'someone in care at the time of the death' were not referred to the Coroner and were not known to us.

Not surprisingly, we were able to firmly establish and confirm that the death was attributed to asthma by examining Coroner's findings, autopsy, toxicology and police reports in 243/283 cases. Twenty six of the cases that were not confirmed were from Western Australia, where we could not obtain permission to examine the relevant documentation. The remaining cases had insufficient information available for a determination to be made.

Living in rural areas however has not been documented to be eventually associated to the related antigens presented in the area. Although 32% of Australians live in rural areas, the data are missing about the prevalence of asthma in this part of the population. In some cities in Europe, asthma prevalence rates are constantly higher in the surroundings and green areas than in the city urban centres. The authors could discuss this further - Is higher prevalence of asthma in Australian rural areas /if it is higher compared to urban ones/ a possible reason for found higher proportion of asthma related deaths in these areas?

We have now commented on the prevalence of asthma being higher in inner city areas in the discussion section of the paper (1st paragraph, page 16) 'A further concern is the higher rate of asthma deaths among those residing in rural or remote areas (45%) given that only 32% of the overall Australian population live in rural or remote areas and asthma prevalence is higher in inner city areas'.

Australian Bureau of Statistics data confirms a relationship between mortality rates and remoteness of residence between 2003-2007. Among those aged 5-34 years the highest death rate occurred in the Outer regional areas whereas for those aged 35-64 years and 65 years and over the highest asthma mortality rate occurred in Remote/Very remote areas. We have added further information in the paper about the higher number of deaths in rural areas and the likely relationship to physical distance and access to health services (1st paragraph, page 16).

The preventable factors are mentioned but it is not clear what preventable factors the authors had in mind. Some recent results support the existence of a genetic basis to the severe asthma phenotype, including asthma-related death, and this could be also mentioned in the discussion session.

It was beyond the scope of our study to investigate physiological/laboratory based research or the existence of genetic basis to the severe asthma phenotype. The purpose of our research was more in the line, with a health service provision/public good approach, and focus to ascertain circumstances surrounding asthma deaths to identify what immediate interventions, if any, could be taken to reduce asthma deaths. Preventable deaths were assessed on the basis of available details, and consensus clinical judgement if different or specific actions had been taken and the death was likely to have been avoided. Modifiable factors associated with the death were factors amenable to change and that may have contributed to the fatal outcome. Genetic factors are rarely preventable.

Table 2.

Despite the authors' explanation, time interval (2005-2009) should be the same for all the studied territories whatever small number of the cases was found in Tasmania, NT and ACT (2005-2010).

All available closed cases for each state and territory between 2005-2009 were examined. However Australian privacy laws state that 'confidentiality must be observed at all times' and small case numbers that may identify individual cases must be aggregated when reported in tables.

The purpose of Table 2 was to demonstrate the overall number of deaths in those over and under 70 years. As most information reported in table 2 features in table 1, and it was confusing to several reviewers, it has been removed and a flow chart detailing the actual number of cases has been included in line with reviewer 2s suggestion.

Minor spelling errors

Page 6, 9: a increase should be an increase; Page 7, 52: The correct name of SPSS Statistical Package ...for Social 'Sciences' and not for 'Scientists'.

We thank the reviewer for drawing our attention to these spelling errors, they have now been corrected.

Reviewer 2

- Line 26 page 6 does not define the population being studied. This needs to be refined (ie as far as I can see, about 20% of all asthma deaths in this time period in Australia (ie 283/1552 cases; I got confused by the numbers of asthma deaths in the text and tables including 1552; 557 and 283 on page 8; Table 2 totals were 563 - suggest add totals to the table))

We have added a sentence (see last paragraph page 7) defining the population studied: 'Cases of asthma deaths in those under 70 years of age and that were deemed to be due to asthma were included in our analysis.'

In order to clarify the number of deaths examined Table 2 has been replaced with a flow chart (see Fig1. Page 9)

- 'Circumstances surrounding the deaths' - I cant see in the methods how this is defined or ascertained - if the medical records were not available, then state how these are based on eg . third part reports from the police and coroners reports.

The last paragraph of the Methods section under Data Collection (page 7) refers to Coroner's findings, autopsy, toxicology and police reports being reviewed to determine if the team agreed the death was due to asthma and whether it was preventable or modifiable factors existed.

The Methods section first paragraph page 8 states: Preventable deaths were assessed on the basis of available details, and consensus clinical judgement if different or specific actions had been taken and the death was likely to have been avoided. Modifiable factors associated with the death were factors amendable to change and that may have contributed to the fatal outcome.

- I got confused regarding the population being studied - in essence 283 cases (? out of 557) identified from the NCIS database of cases reported to the coroner. I suggest this is clarified.

Particularly for a 'non-Australian' reader.

We have incorporated a description, at the beginning of the Methods section (page 6) of the paper, of what constitutes a 'reportable death' and the process of investigation by the coroner. We have also inserted a flow chart (page 9) to clarify the number of cases of asthma death in those under 70 years of age between 2005-2009 (557) and number of cases we examined (283) and the number that were confirmed as asthma deaths (243).

- An intro to the system for certifying and confirming the accuracy of asthma deaths in Australia would help. What training do doctors have in completing death certificates? How is 'Underlying cause of death due to asthma determined? Which sorts of cases are referred to the coroners? Do the coroners do post mortems on all cases referred and what constitutes a post mortem exam - ie is histology always done? Is this quality controlled - eg are the conclusions agreed by more than one coroner?

The research team was not able to access Death Certificates due to Australian Privacy Laws and so accuracy of certification could not be examined in this study.

A 'reportable' death is, a death that is 'unexpected' 'unnatural', 'violent' or the death of someone 'in care' at the time of death.

Usually a police officer or a medical practitioner notifies the Coroner of any death that may be 'reportable', however, any person may notify the Coroner if they believe that a reportable death has occurred. The role of the Coroner is to investigate the circumstances surrounding all 'Reportable deaths'.

At the conclusion of every investigation, it is the task of the Coroner (a single coroner) to prepare a written Finding to establish wherever possible: the identity of the deceased; the circumstances surrounding the death; the cause of death; and the particulars needed to register the death. An autopsy, undertaken by a forensic pathologist, can help explain the cause of death and is part of the coronial investigation into 'reportable' deaths. As the next of kin has a legal right to file an objection to an autopsy being conducted, the Coroner will take into consideration any such objection and therefore an autopsy is not always carried out. Once the pathologist has all the results of the tests, a detailed report is prepared for the Coroner, which outlines medical findings and conclusions. The Coroner takes this information into account when making a finding.

- The authors should define the outcomes more clearly. eg what are possible preventable factors? How did they 'confirm' the asthma deaths? (Page 6 lines 56/57). How did they confirm these people actually had asthma? As far as I can see, the clinical records were not available to this investigation - if so, some detailed analysis could be included in the section on 'Inadequate treatment', page 13.

See last paragraph page 7 'Coroner's findings, autopsy, toxicology and police reports were reviewed by the research team (3 respiratory physicians, a medical sociologist and a research officer).

- Goldacre reference could be included. PDF File attached. (Goldacre MJ, Duncan ME, Griffith M. Death rates for asthma in English populations 1979-2007: Comparison of underlying cause and all certified causes. Public Health. 2012;126(5):386-93.) Suggest include some discussion on accuracy of death certificates.

We thank the Reviewer for the Goldacre reference and have replaced reference 27 with this later reference.

The research team was not able to access Death Certificates due to Australian Privacy Laws and so accuracy of certification was not an issue in this study. See response to Reviewer 1.

- Page 8 line 16 - what is a 'closed case'? Suggest define this term.

The term 'Closed case' has now been defined (see first paragraph page 7) and Results section under the heading DATA on page 9)

My assessment scores above may seem confusing - my difficulty is that the results are clearly written up as is the discussion, however, it took me a while to work out which population were actually studied - and I still dont know if the medical records were utilised in deriving the final conclusions. I can understand the results and the interpretation of these, however, as above the authors do need to improve on the introduction section: to clarify the systems in place in Australia for death certification; to describe the death certification process and the methodology and training of the coroners performing the post mortems in particular.

The research team was not able to access Death Certificates due to Australian Privacy Laws and so accuracy of certification was not an issue in this study.

Details on 'reportable' deaths, deaths examined by the coroner, have now been included at the beginning of the Methods section of the paper.

The study population ie as I can see 20% of the certified asthma death cases in the time period studied should be clearly defined in the Methods section.

The discussion should include details of the quality and robustness of the cases confirmed by the panel as 'underlying asthma deaths'.

A Flow diagram of the number of cases examined has been include in the Results section (see page 9) See Methods section, last paragraph page 7 for detail on how cases were confirmed as asthma deaths 'Coroner's findings, autopsy, toxicology and police reports were reviewed by the research team (3 respiratory physicians, a medical sociologist and a research officer) and first paragraph page 8. See Study Limitations on page 19 in the Discussion section for comment on quality and robustness of the case data.

No Consort Diagram - this would help to address my confusion regarding the study population.

We have added a flow chart (Figure 1, page 9) to assist readers to identify the study population.

Reviewer 3.

3. Is the interpretation (discussion and conclusion) well balanced and supported by the data?

The discussion seems a bit speculative.

Firstly, some comments on the health system of the country studied are needed.

Access to the health system in countries with free universal public health care, like those in Western Europe, is not he same as in others where private insurance predominates, as in the USA.

We have included detail on 'Medicare' a universal public health care system (see first paragraph page 16)

Page 14, line 56- In 243/283 cases, it is believed the cause of death is asthma, as indicated in the Death Registers. This seems to support the high specificity of the death certified as asthma. You could mention this.

We thank the reviewer for this suggestion, and have now mentioned this in the first paragraph of the Discussion section of the paper.

Page 15- line 19- it says “our findings identify disadvantage as an underlying theme among asthma deaths”. However, in the results, it was not analysed if there was a relationship between disadvantage and death due to asthma or preventable death.

We have included additional information in the results section under Socio-economic status on page 12 about the slightly higher number of preventable deaths in those living in areas classified as disadvantaged.

Page 15- line 39- it says “our study confirms higher rates of asthma deaths in those living in areas of disadvantage...”. But this has not been analysed. That the majority of deaths occur in areas of disadvantage does not indicate that there may be a higher risk for asthma here, given that we do not know the prevalence of the disease in these areas, nor does it give the number of inhabitants.

The Australian Centre for Asthma Monitoring (ACAM) have examined this issue. We have included a reference to this publication.

Page 17- Line 3. It says that “deaths occurred in public places indicates rapid onset asthma attacks”. This does not seem to be mentioned by the authors who analysed “rapid-onset attacks” (Plaza V, reference 19; Rodrigo G, reference 18; Kolbe, Thorax 1998). There could have been multiple factors for deaths to occur in public places, besides a rapid-onset attack.

We have re-written the last paragraph of page 17: ‘Our study identified a sub-set of apparently sudden onset asthma with rapid deterioration to death. Kolbe et al, has previously reported that there appears to be a small proportion of people with rapid onset severe asthma who do not demonstrate usual risk factors associated with life threatening asthma and who require different management strategies.¹⁸ The eleven deaths that occurred in public places were consistent with rapid-onset asthma attacks.’

Page 18- line 23. It says “Ownership of written action plans has declined”. However in Results, page 13-line 25- it is stated “It was not possible to determine written action plan ownership from this data set.”

We have amended the results and discussion sections to clarify the limitation of available information about action plan ownership (see 2nd paragraph p.19).

‘Results: It was not possible, in most cases, to determine written action plan ownership from this data set’.

Discussion: Ownership of written action plans has declined, despite their being protective against asthma death⁵ and research reporting ownership as useful.²³ In 2007-2008 less than 20% of the population with asthma were reported to own one.² Education, especially if delivered with a written asthma action plan, will assist in the recognition of asthma exacerbations, appropriate emergency asthma management and seeking care in a timely fashion. The delivery of home-based person-

centred asthma self-management education utilising the recently developed Patient Asthma Concerns Tool (PACT) has also proven successful in those over 50 year of age.²⁶ Although evidence of written action plan ownership and asthma self-management education was available in some cases, unfortunately this information was not available for most.

CONCLUSIONS:

They must be re-written in accordance with that indicated in the Results and Discussion.

For example: Page 19- line 19. It says "Our retrospective study provides a current assessment of death from asthma across Australia.". It should be added that it is among the deaths", given that they may be different from the deaths due to asthma that are not reported by the Coroner.

We have now qualified our conclusion. (First sentence of the Conclusion on page 20). Our retrospective study provides a current assessment of 'reportable' asthma deaths across Australia. Seventy percent of these deaths were considered preventable and our findings suggest that to achieve further reductions...

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work? In this section, it must clearly indicate the period of the study (although it is mentioned in the Results), and the retrospective nature of the study.

It should be clearly explained what information could be consulted, particularly if they are included in the hospital or general practitioner clinical notes. Clearly mention the comorbidities that are considered as exclusion criteria (if there were any).

We have added details of: the period of study, that the study was retrospective and added our Exclusion criteria to the Methods section of the paper. (see first sentence under heading Data Collection on page 7 and Exclusion criteria on page 8)

As mentioned in the Methods section Coroner's findings, autopsy, toxicology and police reports were reviewed. Access to explore Death registrar and the Australian Mortality database for research purposes is forbidden and therefore links to the hospital and general practitioner records of cases were not traceable/citable unless examined by the Coroner and included in his/her findings.

The SEIFA index must be explained for readers of other countries, who are not used to using it.

We have included greater detail on the SEIFA index:
Socio-economic status (SES) was determined using ABS-Socio Economic Indices For Areas (SEIFA) a continuum of advantage (high values) to disadvantage (low values). SEIFA uses a broad definition of relative socio-economic disadvantage in terms of people's access to material and social resources, and their ability to participate in society. Advantage/disadvantage classifications are derived from Census variables related to low income, low educational attainment, unemployment, dwellings without motor vehicles household, high income and tertiary education.¹⁰ SEIFA index scores are standardised to a mean of 1000. A lower score indicated an area of relative disadvantage compared to an area with a score higher than 1000 (See Socio-economic status under Data Analysis Section on page 8)

STATISTICAL ANALYSIS:

Seems a little lacking. A multivariate analysis would provide more information on what really are the significant factors. There could be a correlation between the SEIFA-delay seeking help-illegal drug use- inadequate management index.... Or even with other comorbidities not analysed but may be a known risk factor for a poor prognosis of the asthma (obesity...).

The opinion of a reviewer expert in statistics-epidemiology could be useful.

Because this was a case series, only simple descriptive statistics were appropriate. No multivariate analysis was feasible because of missing data. Even bivariate correlations were likely to be misleading.

5. What are the strengths and weaknesses of the methods?

The main strength of the study is providing toxicological and the post-mortem information, which reinforces the accuracy of the causes of death.

As weak ones, see points 3, 4, 6.

6. Can the writing, organization, tables and figures be improved?

RESULTS:

Almost 50% of the cases are lost. The main reasons for these losses should be explained, since it could lead to a bias.

Also, the toxicology analysis was unavailable in 75 cases (47%). The reasons should be given, since it could lead to inclusion biases.

Table 2 should show the rates, as well as the absolute values. The number of cases acquire a value in relation to the population of each region.

The 50% of cases that were lost were cases not reported to the Coroner. We have included reference to this under study limitations in the Discussion section of the paper (page19..

There is a reference to toxicology reports not being electronically available for examination and therefore actual drug alcohol usage may be higher than stated in our findings in the third paragraph of the Discussion on page 16.

Table 2 was confusing to Reviewers, it has now been removed.

PAGE 10- Line 38: PREVENTABLE DEATHS:

It should be easier to read: ...70% of the cases (169/243) instead of "One hundred and sixty-nine of the 243(70%) cases"

The wording in the paper has been amended accordingly.

A table could be added with the preventable /modifiable factors, at least those with the higher frequencies.

Page 10-Case characteristics.

It would be more useful to present a table comparing the characteristics of the cases with preventable or modifiable factors vs. cases with non- preventable non-modifiable factors, and analysing whether there were significant

differences.
Preventable or
modifiable factors
Non- preventablenon-
modifiable
factors

We have added a table (table 3, page 11) providing information on case characteristics as suggested by the reviewer.

7. When revisions are requested.

I think that:

- data need to be added to support the authors' conclusions
- better justification is needed for the arguments based on existing data
- the clarity and/or coherence of the paper needs to be improved.

We thank the reviewer for these comments and have now made clarifications where requested and provided support to strengthen our conclusions.

9. References:

References are quite old, 50% older than 5 years.

Six of the seven older references report on the seminal Australian asthma mortality studies. We than the reviewer for alerting us to the article by Krantz et al and have updated our reference on illicit drug use by citing this article.

Reference 26 is not required, since it is included in Reference 25.

This reference has now been removed

There are some important (and updated) references lacking, or which could be useful to improve the manuscript.

We thank the reviewer for the list of references. We have referenced the article by Kolbe et al, to add support to our mention of Rapid Onset asthma.

While we read the articles on the accuracy of death certificates with interest, as our study was unable to examine death certificates, we did not feel these references were relevant to our paper.

VERSION 2 – REVIEW

REVIEWER	Francisco-Javier Gonzalez-Barcala Asthma Clinical Research Unit. Clinic Universitary Hospital. Santiago de Compostela-Spain.
REVIEW RETURNED	11-Mar-2013

GENERAL COMMENTS	All my concerns were correctly addressed
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REVIEWER	Dr Mark L Levy FRCGP
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	<p>Senior Clinical Research Fellow, Allergy and Respiratory Research Group, Centre for Population Health Sciences: GP Section, University of Edinburgh. Doorway 3, Medical School, Teviot Place, Edinburgh EH8 9AG United Kingdom.</p> <p>Dr Mark L. Levy- 2013 Potential Conflicts of interests: Dr Mark.L.Levy has accepted sponsorship from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Trinity-Cheisi, Merck Sharpe and Dohme, Merck, Novartis, Meda Pharmaceuticals, 3M Pharmaceuticals, TEVA, Schering Plough and NAPP Pharmaceuticals for attending conferences. He has accepted lecture fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Cheisi and Alk-Abello. He has been on advisory boards or provided consultancy for GlaxoSmithKline, Schering Plough, Merck Sharp and Dohme, Cheisi, Altana Pharma, Ranbaxy, AstraZeneca, TEVA, Clement Clarke and Novartis. He has had research grants from Boehringer Ingelheim, Pfizer, GSK, He is a member of the ADMIT Group, which received an unrestricted educational grant from MEDA pharmaceuticals - up until December 2011, and one grant from Chiesi Pharmaceuticals in October 2012. He was a member of a Data Safety Monitoring Board (DSMB) for the FORWARD Study n° CCD-0906-PR-0016. He is a Board member of the GINA Strategy Group - while he does not receive any remuneration for this latter work, his travel and accommodation expenses are paid to attend the annual 2 day meeting of the board in London each January.. He is currently the Clinical Lead for the United Kingdom National Review of Asthma Deaths.</p>
REVIEW RETURNED	04-Mar-2013

GENERAL COMMENTS	<p>Four minor points:</p> <ul style="list-style-type: none"> • Table 4: Toxicology results: Please add the normal values; the alcohol units in the table and footnote are different. These should be uniform. • Similar comment regarding the reference to alcohol in the discussion: (Page 17 para 1, line 2) • Page 18; para 2: Several deaths were likely due to acute hypersensitivity reactions including beta-blocker eye drops and non-steroidal anti-inflammatory treatments. • Future research page 21: Suggest amend to state that a prospective 'case controlled study' is required.
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